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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,046	09/27/1999	THOMAS MEADE	A-58634-6/RF	9059

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EXAMINER	
JONES, DAMERON LEVEST	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 10/02/2003

29

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/405,046	MEADE ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-30 and 32-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30 and 32-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of Paper No. 28, filed 7/14/03, wherein claims 22, 30, 32, 33, 41, 42, and 46-48 were amended; claim 31 was canceled; and claims 49-58 were added.

Note: Claims 22-30 and 32-58 are pending.

RESPONSE TO APPLICANT'S AMENDMENT/ARGUMENTS

2. The Applicant's arguments filed 7/14/03 (Paper No. 28) to the rejection of claims 22-48 made by the Examiner under 35 USC 102, 103, and/or 112 have been fully considered and deemed persuasive-in-part for the reasons set forth below.

112 Rejections

The 112 rejections are WITHDRAWN for reasons of record in Applicant's response.

102 Rejections

The 102 rejection is WITHDRAWN for reasons of record in Applicant's response.

103 Rejections

I. The 103 rejection over Piwnica-Worms is WITHDRAWN for reasons of record in Applicant's response.

II. The 103 rejection of Gries et al in view of Piwnica-Worms is WITHDRAWN because Piwnica-Worms has a later priority date than that of Applicant.

III. Applicant's arguments with respect to claims 22 and 32 as it relates to the 103 rejection over Gries et al have been considered but are moot in view of the new ground(s) of rejection.

NEW GROUNDS OF REJECTION

112 Rejections

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 42 and 46-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims as written are ambiguous because independent claim 42 is directed to a method but it does not identify the method . Thus, it is unclear if it is a method of imaging or so forth. Hence, Applicant is respectfully requested to clarify the claim in order that one may readily ascertain what is being claimed.

103 Rejections

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 22-30 and 32-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauffer et al (US 2002/0034476 A1) in view of Gries et al (US Patent No. 5,648,063) in further view of Mathews and van Holde (1990, Biochemistry, pages 340-341).

Lauffer et al disclose bioactivated diagnostic imaging contrast agents and uses of the agents (see entire document, especially, abstract; page 22, claim 2). The agents comprise three domains, an imaging-enhancing moiety (IEM) a modification site (MS), and a protein-binding moiety (PBM) [see page 2, paragraphs [0031] – [0032]). A preferred method of bioactivating the contrast agent involves enzymatic cleaving of the prodrug at the MS moiety (page 3, paragraph [0034]). Possible complexes are those set forth on page 3, paragraph [0036] wherein when m = 1, p = 1, o = 0, n = 1; and q = 1 reduces to a complex comprising IEM-PBM-MS such that IEM is a pharmaceutically acceptable metal chelate compound consisting of one or more cyclic or acyclic organic chelating agents complexed to one or more metal ions such as gadolinium (page 4, paragraphs [0051] – [0052]; page 5, paragraph [0060]). Many suitable chelating ligands for MRI known in the art may be used (page 5, paragraph [0062]). Preferably, IEM comprises a DOTA ligand (page 11, paragraph [0111]). The PBM substitutent may be a peptide (page 6, paragraph [0067]). The MS domain on the prodrug is altered by the specific bioactivity desired to be imaged. The alteration, which is a biotransformation (enzymatic or otherwise) such as bon cleavage, bond formation, oxidation, reduction, or protonation/deprotanation, results in the generation of bioactivated agents. It should be noted that the MS substitutent may be an inherent part of the IEM or PBM domains so

long as it does not adversely affect their individual functions (page 8, paragraph [0094]). Preferred MS domains are those that are capable of being altered in vivo by enzymes such as serine proteases and metalloproteinases (page 9, paragraphs [0095] – [0096]; page 10, paragraphs [0100] – [0101]). In addition, Lauffer et al disclose that in order to effectively enhance MRI images the complex is capable of enhancing the relation rates 1/T1 and/or 1/T2 of water protons. Relaxivities R1 and R2 are defined as 1/T1 and 1/T2, respectively, per iM of metal ion. Thus, the relaxivities may be altered to enhance the MRI images (pages 4-5, paragraphs [0056] – [0059]). Furthermore, Lauffer et al disclose that the magnetic resonance phenomena is complex and different paramagnetic materials alter the MRI signal to various degrees. A quantitative measurement of the ability of a contrast agent to relax water protons, and consequently affect the MRI image, is provided by its relaxivity. Relaxivity is the dependence of water proton signal intensity upon the concentration of paramagnetic metal ion in solutions (page 7, paragraphs [0080] – [0081]). While Lauffer et al disclose that DOTA may be conjugated to a peptide, the reference fails to specifically disclose that the DOTA derivative is attached to the peptide via a carboxyl group or R26 as set forth by Applicant.

Gries et al disclose compositions comprising a chelate complex for magnetic resonance imaging. The complexes comprise one or more elements having atomic numbers 21-29, 42, 44, or 57-83 (see entire document, especially, abstract; column 3, lines 49-61; column 5, lines 24-43). Possible biomolecules which may be conjugated to the complexes include peptides and antibodies (column 4, lines 26-32). Conjugation

may occur via a carboxyl group of the complexing acid or by a CH2 group on a protein or peptide (column 4, lines 39-43). In column 23, Example 59, a solution of a gadolinium complex with DOTA and a monoclonal antibody is disclosed. Also, it should be note that Gries et al encompass various DOTA derivatives (column 5, lines 23-35).

Mathew and van Holde disclose the six major classes of enzymes and their functions (see pages 340-341).

It would have been obvious to one of ordinary skill in the art to modify the invention of Lauffer et al using the teachings of Gries et al and Mathews and van Holde and generate MRI agents and uses thereof as set forth in Applicant's independent claims 22, 30, 32, and 42 because Lauffer et al disclose bioactivated diagnostic imaging using contrast agents. Now, while Lauffer et al fail to disclose the specific DOTA complex as set forth in Applicant's independent claims that is linked by either a carboxyl group or Applicant's variable R26, Gries et al (column 4, lines 26-43, especially, 40-43) disclose that the complexing acid (e.g., DOTA derivative) may be conjugated conventionally via a carboxyl group or in the case of peptides, by a lower alkyl group (see R3 in column 1, lines 60-62 of Gries et al). Hence, a skilled practitioner in the art would recognize that Applicant's variable R26 that links the peptide to the DOTA analog (see independent claim 22 for example) may be a lower alkyl linker and the carboxyl group that links the peptide in Applicant's claim 32, for example, is obvious since conjugation can occur conventionally via a carboxyl group of the complexing acid. Mathew and van Holde is cited to show that it is well known in the art to divide enzymes into six major classes: oxidoreductases, transferases, hydrolases, lyases, isomerases,

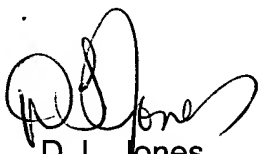
and ligases. Thus, it should be note that all enzymes fall into one of the classes and that the enzymes claimed Lauffer et al (see claims 44 and 45) is directed to the six classes. Hence, all of the proteases set forth by Applicant are also encompassed in the invention of Lauffer et al.

Since both Lauffer et al and Gries et al disclose DOTA complexes that may be used as contrast agents, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



D. L. Jones
Primary Examiner
Art Unit 1616

September 23, 2003